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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/831,629	08/17/2001	Rina Aharoni	AHARONI 5B	6949

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EXAMINER	
LUKTON, DAVID	
ART UNIT	**PAPER NUMBER**
1653	

DATE MAILED: 04/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/831,629	AHARONI ET AL.	
	Examiner	Art Unit	
	David Lukton	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) *6-14 and 16-33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Applicants' election of Group II (claims 1-5 and 15) is acknowledged, as are the species elections [(a) copolymer-1 having all-L amino acids, (b) an average MW of 7 kD, and (c) net positive charge]

Applicants have traversed the restriction by arguing that PCT rules confer "immunity" from restriction. However, applicants are not correct. Consider the following passage (MPEP 1850):

MPEP 1850

PCT Rule 13.2, as it was modified effective 01 July 1992, no longer specifies the combinations of categories of invention which are considered to have unity of invention. Those categories, which now appear as a part of Annex B to the Administrative Instructions, has been substituted with a statement describing the method for determining whether the requirement of unity of invention is satisfied.

Unity of invention exists only when there is a technical relationship among the claimed inventions involving one or more special technical features. The term "special technical features" is defined as meaning those technical features that define a contribution which each of the inventions considered as a whole, makes over the prior art.

The determination is made based on the contents of the claims as interpreted in light of the description and drawings. Annex B also contains examples concerning unity of invention.

Independent and Dependent Claims.
Unity of invention has to be considered in the first place only in relation to the independent claims in an international application and not the dependent claims. By "dependent" claim is meant a claim which contains all the features of another claim and is in the same category of claim as that other claim (the expression "category of claim" referring to the classification of claims according to the subject matter of the invention claimed for example, product, process, use or apparatus or means, etc.).

If the independent claims avoid the prior art and satisfy the requirement of unity of invention, no problem of lack of unity arises in respect of any claims that depend on the independent claims. In

particular, it does not matter if a dependent claim itself contains a further invention. Equally, no problem arises in the case of a genus/species situation where the genus claim avoids the prior art. Moreover, no problem arises in the case of a combination/subcombination situation where the subcombination claim avoids the prior art and the combination claim includes all the features of the subcombination.

If, however, an independent claim does not avoid the prior art, then the question whether there is still an inventive link between all the claims dependent on that claim needs to be carefully considered. If there is no link remaining, an objection of lack of unity (that is, arising only after assessment of the prior art) may be raised. Similar considerations apply in the case of a genus/species or combination/subcombination situation.

It is clear that claim 1 does not "define a contribution" over the art, at least for the reasons given below. Accordingly the restriction is still deemed to be proper. Nevertheless, in the event that one or more composition claims are found to be allowable, the corresponding method of use claims will be rejoined therewith, provided also that whatever limitations are introduced into the composition claims will also be introduced into the method claims. Among these limitations would be: (a) specific limitations on the copolymer itself, and (b) the requirement, in the method claims, that it is a composition (comprising a carrier and the copolymer) that is used, and not the peptide itself. It is suggested, in fact, that the method claims be amended along with the composition claims, in response to each Office action.

✧

35 U.S.C §101 reads as follows:

"Whoever invents or discovers any new and useful process, machine, manufacture or composition of matter or any new and useful improvement therof, may obtain a patent therefore, subject to the conditions and requirements of this title".

Claims 1-5 and 15 are rejected under 35 USC §101 because the claimed invention is not supported by a well established utility.

The claims recite that GVDH (and HVGD) can be "prevented". However, there is no evidence that this is the case. The term "prevention" implies that not a single test subject exhibits any symptoms of the disease at all. The "bar" that must be overcome in showing this is quite high. For example, suppose that one of the claimed compounds were administered to each of 10,000 rats. Suppose further that of these 10,000 rats, 9,999 of them failed to develop symptoms of GVDH (or HVGD) as a consequence of being administered the compounds, but that one of the 10,000 rats did develop mild symptoms. Such a result would be considered very successful by any standard. Such a result, however, would actually constitute evidence of "failure" insofar as prevention is concerned. It is suggested that the term "preventing" be deleted from claims 1 and 5.

Claims 1-5 and 15 are also rejected under 35 USC §112 first paragraph. Specifically, since the claimed invention is not supported by a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

✧

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5 and 15 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants have shown that copolymer-1 can be used to treat GVDH. However, copolymer-1 is excluded from the claims. Thus, none of the compounds within the claimed genus has been tested in any assay. One cannot extrapolate from results with COP-1 to other random polymers. Minor structural alterations can eliminate activity; "undue experimentation" would be required to determine which copolymers will be effective.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this action.

A person shall be entitled to a patent unless -

> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1 and 15 are rejected under 35 U.S.C. §102(b) as being anticipated by Carney (USP 5,500,412).

Carney discloses (col 15, line 32+) a pharmaceutical composition that contains the tetrapeptide R-G-D-A.

Arginine meets the requirement for claim 1, part (a), glycine meets the requirement for claim 1, part (c), and aspartic acid meets the requirement for claim 1, part (b).

The first point is that there is no lower limit to the molecular weight of the copolymer. Accordingly, tetrapeptides would be included.

The second point concerns the requirement that the order of amino acids be "random". The examiner contends that this condition is met also. Suppose that one took a deck of cards, and on the face of 13 of those cards, the word "arginine" were written. Suppose that this process were repeated for each of the three remaining amino acids. The deck of cards is then shuffled. If four cards were "dealt" from the deck, there is a significant probability that one of the four cards would have the word "arginine" written

on it, one of the cards would have the word "glycine" written on it, etc. Furthermore, if one were to "deal" all of the cards in the deck (in groups of four), reshuffle the deck, deal the cards, and repeat the process, it would not take long before the sequence "Arg", "Gly", "Asp", "Ala" would come up.

Certainly, Carney prepared the amino acid sequence by design, not by chance. However, that is not the end of the analysis. The question is, was the peptide chosen by Carney equivalent to a peptide that would be obtained by random selection of amino acids? As illustrated by the "card" analogy above, there is a finite probability that if one started with the four amino acids in question, and prepared tetrapeptides at random, the disclosed peptide would be obtained. The claims are drawn to peptide compositions. The claims are not drawn to a method of selecting a sequence. If the claims were drawn to a method of selecting an amino acid sequence, the analysis might be different. But as the claims currently stand, they are anticipated.

Applicants' traversal of the restriction requirement (page 4, response filed 2/20/04) suggests that applicants might make the argument that claim 1 mandates that both of the following conditions be met: (a) the term "copolymer" mandates that one have a mixture of different peptides, and (b) the different peptides within the mixture must occur within a range of molecular weights. Although this argument has not yet been made, the examiner would argue that the claims impose no such requirements on the term "copolymer".

A copolymer of amino acids is a peptide containing amino acids. If the "copolymer" is limited to certain specific amino acids, then the peptide will consist only of those amino acids. But a peptide which contains amino acids does not lose its property of being such merely because it is a pure compound. The same is true of a copolymer. If one has a single pure compound, and if that compound happens to be a copolymer, then the property of being a copolymer is not lost merely because the compound is pure. If applicants want to mandate that a mixture of peptides, and/or a mixture of molecular weights is present, that would be applicants' prerogative to do so. But as the claims currently stand, the term "copolymer" would include a single, pure peptide.

Thus, the claims are anticipated.

✧

Claims 1 and 15 are rejected under 35 U.S.C. §102(b) as being anticipated by Komazawa (USP 6,046,289).

Komazawa discloses various copolymers prepared from propenamide derivatives of RGD peptides. Pharmaceutical compositions are also disclosed.

The arginine meets the requirement of instant claim 1, part (a), the glycine meets the requirement of instant claim 1, part (c), and the aspartic acid meets the requirement of instant claim 1, part (b).

The issue here concerns the word "random". It is acknowledged that the sequence

RGD was selected by design, and not by chance. However, it is also true that there is a random nature to the polymers that were prepared. The randomness arises because different monomers are being copolymerized, and so the exact sequence (and molecular weight) cannot be predicted or controlled.

Accordingly, the copolymers of Komazawa qualify as "random".

Thus, the claims are anticipated.

✧

Claims 1 and 15 are rejected under 35 U.S.C. §102(b) as being anticipated by Gaffar (USP 4,339,431).

Gaffar discloses copolymers of glutamic acid, tyrosins and alanine; pharmaceutical compositions are also disclosed. Thus, the claims are anticipated.

✧

The following is a quotation of 35 USC §103 which forms the basis for all obviousness rejections set forth in the Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an

obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made, absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103.

Claims 1-5 and 15 rejected under 35 U.S.C. §103 as being unpatentable over Aharoni (USP 5,858,964).

Aharoni discloses copolymer-1 and compositions containing it.

This rejection is not imposed under 35 USC §102 because of the following phrase in claim 1:

"the random copolymer is not Cop-1... when the disease... is GVHD"

This rejection, however, is justified for each of three separate, independent reasons:

First, the disclosed peptide could be used to treat host versus graft disease, rather than graft versus host disease. A comparison of instant claim 1 with claim 5 indicates that applicants see a distinction between these two; as a consequence of this distinction, the exclusion of claim 1 is circumvented. At the same time, however, it would have been obvious to one of ordinary skill that a compound which is effective to treat GVDH will be effective to treat HVGD. Thus, the claims are rendered obvious on that basis.

Second, it may be the case (or may not) that copolymer-1 is itself excluded from claim 1.

But what is not excluded is a peptide in which a single Lys, Arg, Glu, Ala, Tyr or Trp residue is replaced with a corresponding homolog differing by one methylene unit. For example, suppose that one had the following (so-called) "GLAT" peptide:

E-K-A-Y-Y-A-E-**K**-A-A-Y-E-K-K-A-E

Compare this with the following ("O" represents ornithine):

E-K-A-Y-Y-A-E-**O**-A-A-Y-E-K-K-A-E

A peptide biochemist of ordinary skill would have expected, *a priori*, that when a side chain of one amino acid in a peptide is extended by one methylene unit, the biological activity of that peptide will remain substantially the same [*In re Shetty* (**195** USPQ 753) and *In re Hass & Susie* (**60** USPQ 544)]. The peptide that contains the ornithine is not copolymer-1, and so the proviso in claim 1 is circumvented. Thus, the claims are rendered obvious on this basis.

Third, the proviso in claim 1 is meaningless anyway, since the claims are drawn to compositions and not a method of use. What is quite obvious to any organic chemist is that when a compound is synthesized, it is stored in a vial while awaiting future use. Maybe the intention is to treat GVDH. Maybe the intention is to conduct *in vitro* experiments. Or maybe the intention is to use the polymer in a cleaning solution.

Whatever the intention, if the polymer is sitting in a vial, it is not being used to treat anything. Accordingly, when the copolymer is present in a vial, the claims are rendered obvious.

Thus, for each of three separate, independent reasons, the claims are rendered obvious.

✧

Claims 1-5 and 15 are rejected under 35 U.S.C. §103 as being unpatentable over The Sigma Catalog, 1991 Edition, pages 1045-1050.

The Sigma catalog lists various bioactive peptides, many of which are no doubt known to applicants. The Sigma catalog does not suggest combining the peptides with a pharmaceutically acceptable carrier, but this would have been obvious to one of ordinary skill, given their pharmacological activity.

Claim 1 recites that the copolymer "comprises" the indicated amino acids. This term "comprises" means that the copolymer is not limited to the eight amino acids listed. At a minimum, all 20 genetically encoded amino acids would be included. Accordingly the issue here is what is meant by a "random copolymer". Consider the following two peptides, both of which are well known to peptide chemists:

Dynorphin A (porcine), which has the following sequence:

YGGFLRRIRPKLKWDNQ

Adrenocorticotropic hormone, which has the following sequence:

SYSMEHFRWGKPVGKKRRPVKVYPNGAEDESAEAFPLEF

Both of these peptides contain the requisite amino acids from part (a), (b), (c) and (d) of claim 1. No doubt applicants will argue that these peptides are not "random". However, applicants would not be correct. According to scientific explanations of evolution, life itself started as a consequence of random events which gave rise to the basic building blocks of life such as nucleotides, amino acids, lipids, etc. Evolution then occurred as a consequence of random genetic alterations (or mutations) which in turn gave rise to peptides and proteins that did not previously exist. According to theory, those alterations (or mutations) which permitted organisms to flourish were retained in the species, and those alterations which provided no advantage (or even disadvantage) were not propagated because of "natural selection". Thus, according to evolutionary theory, all polynucleotides, peptides and proteins arose as a result of random genetic alterations. Included among those peptides and proteins would be, for example, adrenocorticotropic hormone and dynorphin A.. One can, of course, synthesize these peptides by a decidedly non-random process. But the fact that they may be synthesized by design, rather than by chance, does not change the analysis. The fact is that, once synthesized, they are equivalent to peptides that arose from (ostensibly) "random" events.

The term "copolymer" does not require that one have a mixture of peptides; the term

"copolymer" does encompass the possibility of having one single, pure peptide. Thus, if one synthesizes a single, pure peptide that is equivalent to one which has arisen as a result of random events, the quality or state of "randomness" is met.

It may be the case that this ground of rejection can be overcome by reciting the following (no determination has been made as to what might, or might not constitute new matter):

> *wherein said copolymer is prepared by a process comprising the step of simultaneously combining suitably protected N-carboxyanhydrides of the amino acids.*

Note the presence of the term "simultaneously". Absent this term, the rejection could still be maintained. The reason is that one can synthesize almost any peptide (by design) by sequentially adding N-carboxyanhydrides of amino acids to a growing peptide chain.

As the claims now stand, however, they are rendered obvious.

✧

Claims 1-5 and 15 are rejected under 35 U.S.C. §103 as being unpatentable over The Sigma Catalog, 1991 Edition, pages 1045-1050 in view of Wagner (*Introduction to Statistics*, pages 82-140, Harper Collins Publishers, 1992).

As indicated above, the Sigma catalog lists various bioactive peptides, such as Dynorphin A and adrenocorticotropic hormone. Also as indicated above, the issue here is what is meant by "random". Suppose that one took each of the twenty encoded amino acids (i.e., A, C, D, E, F, G, H, I, K, L, M, N, P, Q, R, S, T, V, W, Y) and assigned numbers to them, so that alanine would be assigned the number one, cysteine the number 2, etc. The question of whether a

particular sequence is random or non-random would then be reduced to an issue of probability and statistics. Consider, for example, the following "GLAT" peptide:

E-K-A-Y-Y-A

Using the number assignments above (glu being 4, Lys being 9, etc.), this peptide can be assigned the following numerical sequence: 4-9-1-20-20-1

Thus, suppose that one wrote the numbers 1 through 20 on pieces of paper, put the pieces of paper in a container, and then withdrew them one by one. What is the probability that the numbers 4-9-1-20-20-1 would come up in the indicated sequence? A reading of the Wagner reference will provide some insight into this. Similarly, if one were to select (suitably protected) amino acids at random, and condense them one by one, there is a finite probability that the peptide E-K-A-Y-Y-A would arise. There is also a finite probability that e.g., the peptide dynorphin would arise. The fact that a given peptide may be synthesized by design does not detract from the fact that it is equivalent to a peptide that was, or could have been selected at random. Accordingly, the term "random", in the context of claim 1, is not necessarily meaningful.

Thus, the claims are rendered obvious.

✱

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 571-272-0952. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at 571-272-0951.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

DAVID LUKTON
PATENT EXAMINER
GROUP 1600